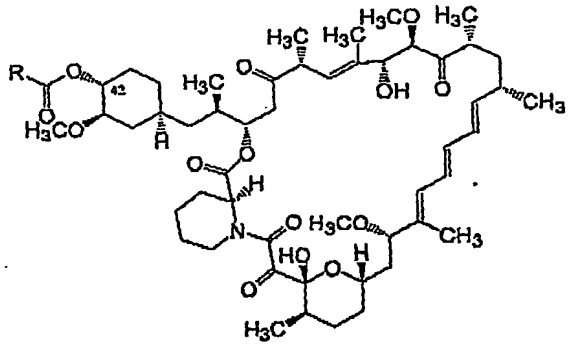
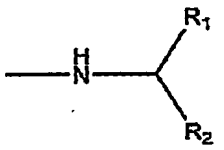
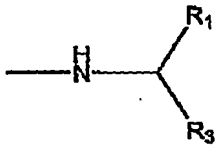


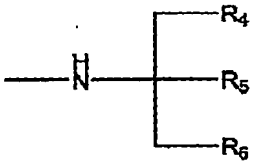
I

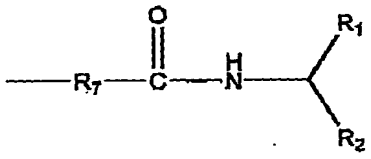
wherein,

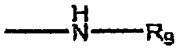
R is NH-$(A)_n$-CH_2OH;











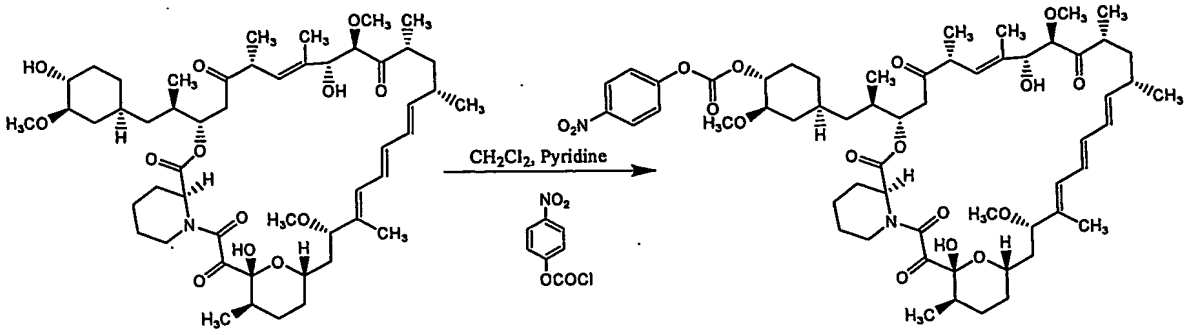
A is *D* or *L* amino acid and n=1-10,

R_1 and R_2 are each independently, hydrogen, alkyl of 1-6 carbons atoms, hydroxyalkyl of 1-6 carbon atoms, or CO_2R_8,

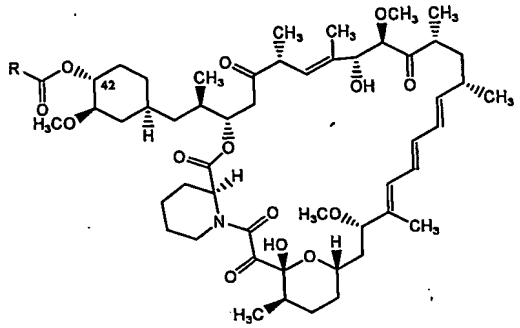
R_3 is Ar, wherein Ar is aromatic or heteroaromatic;
R_4, R_5 and R_6 are each independently alkyl of 1-6 carbon atoms or hydroxyalkyl of 1-6 carbon atoms;
R_7 is alkyl of 1-10 carbon atoms;
R_8 is alkyl of 1-6 carbon atoms; and
R_9 is cycloalkoxyalkyl of 4-10 carbon atoms;
wherein R and said compound of formula I are linked through a carbamate ester linkage.

In one embodiment, amino acids and/or small peptides derivatives of the octapeptide HSKRRLIF are conjugated with rapamycin (formula **5**). The regioselective synthesis of derivatives of rapamycin **5** at the 42 position, is achieved by conjugating the amino end of the amino acids and/or active peptides with 42-O-(4-Nitrophenoxycarbonyl) rapamycin (**6**). Compounds of general formula **7** (**Scheme 1**) are thereby obtained.

Scheme 1



5 6



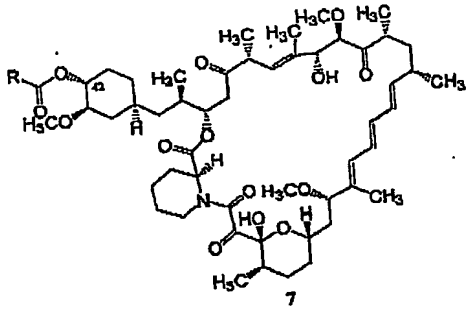
7

The peptides conjugated to rapamycin preferably comprise amino acids from the C-terminal of the octapeptide HSKRRLIF. The amino acids at the N-terminal may differ from that of the octapeptide. Single amino acids may also be used. Examples of compounds obtained by the combination of 42-O-(4-Nitrophenoxycarbonyl) rapamycin and amino acids and/or peptides are given below (compounds 7a to 7v).

The peptides used to derive 42-O-(4-Nitrophenoxycarbonyl) rapamycin can be synthesized from amino alcohols. The first amino acid is kept as Phe-OH (or 2-amino-3-phenyl-propanol) and performing chain elongation with Fmoc chemistry in solution phase (**Scheme 2**) using DCC/HOBt as the coupling reagents.

alcohols. Compounds 7j to 7v are examples of such amino alcohols-rapamycin conjugates(Sheet 1).

Sheet 1



7

7a NH-*L*-Ile-*D*-Phe-CH_2OH

7b NH-*L*-Ile-*S*-Phe-CH_2OH

7c NH-*L*-Leu-*L*-Ile-*D*-Phe-CH_2OH

7d NH-*D*-Leu-*L*-Ile-*S*-Phe-CH_2OH

7e NH-*L*-Ala-*L*-Leu-*L*-Ile-*D*-Phe-CH_2OH

7f NH-*D*-Ala-*D*-Leu-*L*-Ile-*S*-Phe-CH_2OH

7g NH-N-Im(Trityl)*D*-His-*L*-Ala-*L*-Leu-*L*-Ile-*D*-Phe-CH_2OH

7h NH-N-Im(Trityl)*D*-His-*L*-Ala-*L*-Leu-*L*-Ile-*D*-Phe-CH_2OH

7i NH-*L*-His-*L*-Ala-*L*-Lys-*L*-Arg-*L*-Arg-*L*-Leu-*L*-Ile-*D*-Phe-CH_2OH

7j R = $HO\text{-}CH_2\text{-}CH(NH\text{-})\text{-}CH_2C_6H_5$

7k R = $HO\text{-}CH_2\text{-}CH(NH\text{-})\text{-}CH_2C_6H_5$

7l R = $HO\text{-}CH_2\text{-}CH(NH\text{-})\text{-}CH(OH)C_6H_5$

7m R = $HO\text{-}CH_2\text{-}CH(NH\text{-})\text{-}CH(CH_3)\text{-}CH_2CH_3$

7n R = $HO\text{-}CH_2\text{-}CH(OH)\text{-}CH_2\text{-}NH\text{-}$

7o R = $HO\text{-}CH_2\text{-}CH(NH\text{-})\text{-}CH_2OH$

7p R = $HO\text{-}CH_2\text{-}CH(CH_3)\text{-}CH(NH\text{-})\text{-}CH_2OH$

7q R = $HO\text{-}CH(CH_3)\text{-}CH(NH\text{-})\text{-}CH_2OH$

7r R = $HO\text{-}CH(CH_2NH\text{-})\text{-}CH\text{-}CH_2OH$

7s R = $H_3C\text{-}CH(CH_3)\text{-}CH_2\text{-}CH(NH\text{-})\text{-}CH_2OH$

7t R = $H_3C\text{-}CH(CH_3)\text{-}CH_2\text{-}CH(NH\text{-})\text{-}CH_2OH$

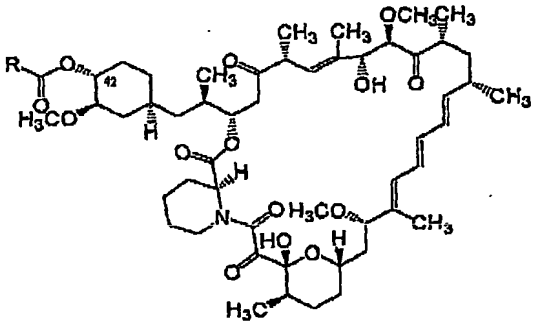
7u R = $HO\text{-}CH_2\text{-}C(CH_2OH)\text{-}CH_2\text{-}NH\text{-}$

7v R = $HO\text{-}CH_2\text{-}CH(NH\text{-}CO\text{-}CH_2CH_2CH_3)\text{-}CH_2C_6H_5$

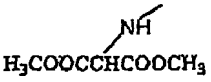
The conjugations of rapamycin with amino alcohols or peptides comprising an amino alcohol at the "C" terminal of the peptide provides increased hydrophilic character to the compound by virtue of the presence of the free hydroxyl group.

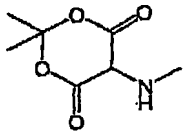
Other rapamycin conjugates (7w, 7x, 7y) exhibiting increase hydrophilicity are shown in sheet 2 below.

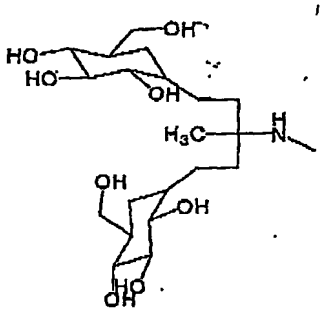
Sheet 2



7

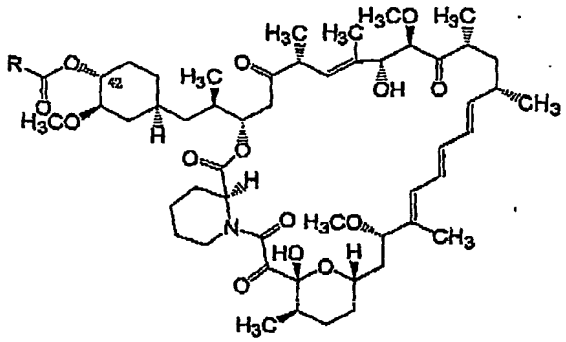
7w R= 

7x R= 

7y R= 

I/WE CLAIM:

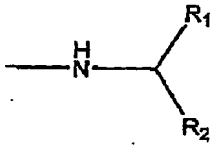
1. A compound of the formula

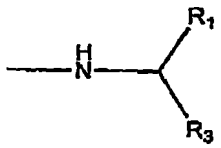


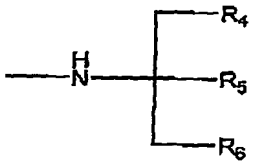
I

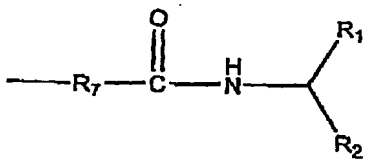
wherein,

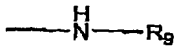
R is $NH-(A)_n-CH_2OH$; or











wherein R as defined above comprises an amino acid; an amino alcohol or a peptide;

A is *D* or *L* amino acid and n=1-10,

R_1 and R_2 are each independently, hydrogen, alkyl of 1-6 carbons atoms, hydroxyalkyl of 1-6 carbon atoms, or CO_2R_8,

R_3 is Ar, wherein Ar is aromatic or heteroaromatic;

R_4, R_5 and R_6 are each independently alkyl of 1-6 carbon atoms or hydroxyalkyl of 1-6 carbon atoms;

R_7 is alkyl of 1-10 carbon atoms;

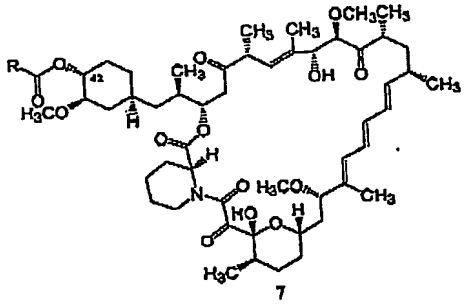
R_8 is alkyl of 1-6 carbon atoms; and

R_9 is cycloalkoxyalkyl of 4-10 carbon atoms;

wherein R and said compound of formula I are linked through a carbamate ester linkage.

2. The compound as claimed in claim 1 wherein R is selected from:

Sheet 1



7

7a NH-*L*-Ile-*D*-Phe-CH_2OH

7b NH-*L*-Ile-*S*-Phe-CH_2OH

7c NH-*L*-Leu-*L*-Ile-*D*-Phe-CH_2OH

7d NH-*D*-Leu-*L*-Ile-*S*-Phe-CH_2OH

7e NH-*L*-Ala-*L*-Leu-*L*-Ile-*D*-Phe-CH_2OH

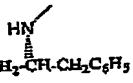
7f NH-*D*-Ala-*D*-Leu-*L*-Ile-*S*-Phe-CH_2OH

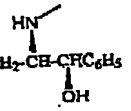
7g NH-N-Im(Trityl)*D*-His-*L*-Ala-*L*-Leu-*L*-Ile-*D*-Phe-CH_2OH

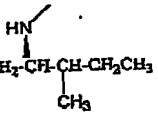
7h NH-N-Im(Trityl)*D*-His-*L*-Ala-*L*-Leu-*L*-Ile-*D*-Phe-CH_2OH

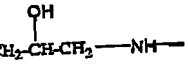
7i NH-*L*-His-*L*-Ala-*L*-Lys-*L*-Arg-*L*-Arg-*L*-Leu-*L*-Ile-*D*-Phe-CH_2OH

7j 

7k 

7l 

7m 

7n 

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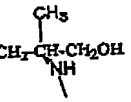
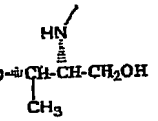
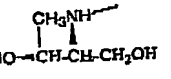
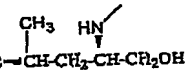
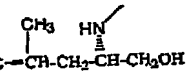
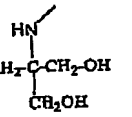
7p 

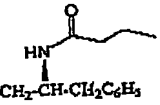
7q 

7r 

7s 

7t 

7u 

7v 

3. A pharmaceutical composition comprising the compound as claimed in claim 1 or 2, or a pharmaceutically acceptable salt thereof, and a pharmaceutically

acceptable carrier for use in treating cell proliferation disorders.

4. A method for treating a cell proliferation disorder comprising administering the pharmaceutical composition as claimed in claim 3 to a patient in need thereof in an amount sufficient to reduce cell proliferation.

5. The method as claimed in claim 4 wherein said cell proliferation disorder is selected from cancer, hyperplasia, psoriasis and hyperproliferative vascular disease.

6. The method as claimed in claim 5 wherein said hyperproliferative vascular disease is restenosis.

7. The method as claimed in claim 5 or 6 wherein said composition is released from a carrier, said carrier being implanted at a desired location within said patient.

8. The method as claimed in claim 7 wherein said carrier is implanted using a vascular guiding means.

9. The method as claimed in claim 8 wherein said vascular guiding means is a cathether.

10. A stent coated with the compound of claim 1 or 2 or the composition of claim 3.

11. The stent as claimed in claim 10 wherein said compound or composition is comprised within a coating composition.

12. The stent as claimed in claim 10 or 11 for treating a hyperproliferative vascular disease.

13. The stent as claimed in claim 12 wherein said hyperproliferative vascular disease is restenosis.

14. A pharmaceutical composition comprising the compound as claimed in claim 1 or 2, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier for use as an immunosuppressant.

15. A method for treating an immunological condition comprising administering the pharmaceutical composition as claimed in claim 14 to a patient in need thereof in an amount sufficient to suppress the immune system.

16. The method as claimed in claim 15 wherein said immunological disorder is selected from autoimmune disease and host-graft disease.

17. A process for the preparation of the compound of claim 1 or 2 comprising reacting 42-O-(4-Nitrophenoxycarbonyl)rapamycin and an amino acid or a peptide or an amino alcohol under basic conditions.

18. The process as claimed in claim 17 wherein said base is pyridine.